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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,857	ARMOUR ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-29,31-33,35,37-42,44 and 46-49* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-29,32,33,35,37-42,44 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/26/04 has been entered.

2. The request for a personal interview prior to next Office Action filed 1/26/04 is acknowledged. A telephone call was made to Mary Wilson on June 15, 2004 to set up an appointment. However, a return call was made to the Examiner on June 18 that a personal interview is not necessary at this time and in favor of First Action on Merit.

3. Claims 16-29, 31-33, 35, 37-42, 44, and 46-49 are pending.

4. Claim 31 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention. Further, said claim fails to comply with the requirement of 37 C.F.R. 1.821(a), SEQ ID NO is required for said claim. Appropriate correction is required.

5. Claims 16-29, 32-33, 35, 37-42, 44, and 46-49 drawn to a binding molecule, polynucleotide encoding said binding molecule, host cell, process of making said binding molecule and a method of using said binding molecule are being acted upon in this Office Action.

6. Claim 42 is objected to under 37 CFR 1.821(d) because SEQ ID NO is required.

7. Claims 17-18, 22, and 24-29 are objected to because "A" should have been "the" for said dependent claims.

8. Claim 32 is objected to because "235A **and** 236G **and** 327G".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 16-29, 32-33, 35, 37-42, 44, and 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated nucleic acid comprising the nucleotide sequence encoding the effector domain of the binding molecule wherein the effector domain is SEQ ID NO: 3 or SEQ ID NO: 12; (2) An isolated nucleic acid comprising a nucleotide sequence encoding a binding molecule wherein the binding molecule is a recombinant polypeptide comprising (i) a binding domain capable of binding to RhD antigen (Fog-1) or CAMPATH-1 (CD52) and (ii) an effector domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 4 wherein the binding molecule is capable of binding said target molecule without triggering significant complement dependent lysis by comparison with human immunoglobulin heavy chain CH2 domain or cell mediated destruction of the target and wherein the effector domain is capable of binding FcγRIIb, and optionally FcRn with reduced affinity for FcγRI, FcγRIIa and FcγRIII; (3) an isolated host cell comprising said nucleic acid; (4) a vector comprising said nucleic acid wherein the nucleotide sequence is operably linked to a promoter; (5) a process for producing a binding molecule, the process comprising the step of growing the host cell transformed with the vector mentioned above under suitable conditions for the expression of said binding molecule; (6) a binding molecule wherein the binding molecule is a recombinant polypeptide comprising (i) a binding domain capable of binding to RhD antigen (Fog-1) or CAMPATH-1 (CD52) and (ii) an effector domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 4 wherein the binding molecule is capable of binding said target molecule without triggering significant complement dependent lysis by comparison with human immunoglobulin heavy chain CH2 domain or cell mediated destruction of the target and wherein the effector domain is capable of binding FcγRIIb, and optionally FcRn with reduced affinity for FcγRI, FcγRIIa and FcγRIII and (7) a composition comprising the binding domain capable of binding to RhD antigen (Fog-1) or CAMPATH-1 (CD52) and (ii) an effector domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 4 wherein the binding molecule is capable of binding said target molecule without triggering significant complement dependent lysis by comparison with human immunoglobulin heavy chain CH2 domain or cell mediated

destruction of the target and wherein the effector domain is capable of binding FcγRIIb, and optionally FcRn with reduced affinity for FcγRI, FcγRIIa and FcγRIII and a pharmaceutically acceptable carrier for inhibiting monocyte activation, complement mediated lysis and ADDC of target cell, **does not** reasonably provide enablement for (1) all isolated nucleic acid encoding all binding molecules as set forth in claims 16-19, (2) host cell as set froth in claim 20, (3) a method for producing any or all binding molecule by *modifying* any or all nucleotide sequence as et forth in claims 21-22, (4) any or all binding molecule as set forth in claims 32-33, 35, 37-39, 41-42, and 44, 46-48, (5) any pharmaceutical composition comprising any or all binding molecule as set forth in claims 40 and 49, (6) a method of binding all target molecule comprising contacting any target molecule as set forth in claims 23-27 and (7) a method of treating all disorder such as the ones recited in claim 28 using all binding molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two binding molecules comprising a binding domain selected from the group consisting of CD52 and FOG-1 (RhD antigen on RBC) and an effector domain wherein the CH2 domain is SEQ ID NO: 3 or 12 as shown in Figure 17 and has reduced affinity for FcγRI, FcγRIIa or FcγRIII, a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The specification further discloses the effector domain consisting of CH2 domain from human immunoglobulin IgG1 substituting for CH2 domain from either IgG2 or IgG4 wherein the amino acid residue E at position 233 of CH2 domain of human IgG1 is substituted for P where P corresponds to the position 233 of the CH2 domain of human IgG2. The amino acid residue L at position 234 of CH2 domain of human IgG1 is substituted for V where V corresponds to the position 234 of the CH2 domain of human IgG2. The amino acid residue L at position 235 of

CH2 domain of human IgG1 is substituted for A where A corresponds to the position 235 of the CH2 domain of human IgG2. The amino acid residue G at position 236 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 236 of the CH2 domain of human IgG4. As an alternative, the amino acid residue G at position 236 of CH2 domain of human IgG1 is deleted since G corresponds to the position 236 of the CH2 domain of human IgG2 is lacking. The amino acid residue A at position 327 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 327 of the CH2 domain of human IgG2. The amino acid residue A at position 330 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 330 of the CH2 domain of human IgG4. The amino acid residue P at position 331 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 331 of the CH2 domain of human IgG4 (See Figure 15). The specification defines binding domain may derive from the same source or a different source to the effector domain wherein binding domain may bind to any target (e.g. carbohydrate, lipid such as phospholipids or nucleic acid (See page 15, lines 6-12). The specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21).

Other than the specific binding molecule mentioned above, the specification does not teach how to make *all* binding molecules (claims 32-33, 35, 37-39, 41-42, and 44, 46-48) and pharmaceutical composition comprising all binding molecules (claims 40 and 49). Let alone a method for treating all disease (claim 28) because of the following reasons.

First, there is insufficient guidance as to the *binding specificity* of all binding molecule or the target to which all the binding molecule bind. Second, there is insufficient guidance about the structure of the "effector domain", the "chimeric domain", the "two or more human CH2 domains", and "the binding molecule" without the amino acid sequence (claims 32, and 41). Third, there is insufficient guidance as to which combination of "at least one amino acid" within which "region of the CH2 domain" of which human immunoglobulin has been modified by amino acid substitution, deletion, or addition to the corresponding amino acid from which second, different human immunoglobulin heavy chain CH2 domain such that the resulting effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII by comparison to which first or second human immunoglobulin heavy chain CH2 domains (claim 35). Fourth, there is insufficient guidance as to which combination of "at least one amino acid" within which "region of the CH2 domain" of which human immunoglobulin has been modified by amino acid

substitution, deletion, or addition to the corresponding amino acid from which second, different human immunoglobulin heavy chain CH2 domain that the effector domain has a reduced complement lysis by comparison to which first or second human immunoglobulin heavy chain CH2 domains (claim 35).

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Without the amino acid sequence, one skill in the art cannot make, much less use the claimed invention.

Kuby *et al*, of record, teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Since the *binding specificity* of the binding molecule, the amino acid sequence of the "binding molecule" and the "effector domain" are not enabled, it follows that the nucleotide sequence encoding the effector domain (claim 16), the binding molecule (claim 17) without nucleic acid sequence are not enabled. Fifth, the specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21). However, the cDNA, RNA, genomic DNA or modified DNA encoding the claimed binding molecules are not disclosed, much less cDNA, RNA, genomic DNA and modified nucleic acid or nucleic acid analog encoding all binding molecules. Since the nucleic acid sequence encoding the effector doain or the binding molecule are not enable, it follows that the vector and host cell comprising said undisclosed nucleic acid sequence encoding all binding molecule are not enabled. In addition to the lack of guidance as to structure of nucleotide sequence encoding all the binding molecule, there is insufficient guidance as to which nucleotides that corresponds to which 2, 3 or 4 amino acids in which first human immunoglobulin heavy CH2 domain in at least which one region such as 233-236 and 327-331 of which CH2 domain to be modified to corresponds to which nucleotides corresponding to which amino acids from which second human immunoglobulin. The recitation of the EU numbering system without the amino acid sequence and/or nucleotide sequence has no structure. Further, there is insufficient guidance as to which amino acids, the corresponding nucleotides to be substitute for which undisclosed amino acids, the corresponding nucleotides and whether the resulting effector domain of the binding molecule maintains its structure and functions. Given the indefinite

number of binding molecules, there is insufficient working examples demonstrating that all undisclosed binding molecule having various amino acids substitution at the CH2 domain would bind FcγRIIb and cause inhibition of one or more B cell activation, mast cell degranulation, or phagocytosis. Further, there is insufficient working example demonstrating that the claimed method of using all undisclosed binding molecule could prevent, inhibit, or interfere with the binding of any undisclosed second binding molecule such as any antibody to which target molecule. Further, there is a lack of in vivo working example demonstrating all undisclosed binding molecule could treat all disorders such as graft-vs-host disease, host-vs-graft disease, organ transplant rejection, bone-marrow transplant rejection, all autoimmune disorder such as vasculitis, autoimmune haemolytic anaemia, autoimmune thrombocytopenia, arthritis, fetal/neonatal alloimmune thrombocytopenia, asthma, allergy, all chronic acute inflammatory disease such as Chrohn's, HDN, Goodpastures, sickle cell anaemia, and coronary artery occlusion.

Even if the binding molecule wherein the binding domain is limited to CD52 and FOG-1 and the effector domain is limited to SEQ ID NO: 1-3, the specification discloses on page 55 line 46 that "the effect of mutations cannot always be predicted from wildtype antibody activities but will depend on the novel context (based on 'mixed' subclasses of IgG) in which the mutation is present". The specification further discloses that the binding molecule wherein the effector domain such as G1Δb (SEQ ID NO: 1) and G1Δc (SEQ ID NO: 2) have 50 to 10 fold lower complement mediated lysis, respectively, although both G1Δb (SEQ ID NO: 1) and G1Δc (SEQ ID NO: 2) bind to the receptor FcγRII equally (See page 55, last full paragraph).

Mogan *et al* (PTO 1449) teach that changing the Leu235 to Glu in the N-terminal end of the C_H2 domain abolished FcγRI binding and unexpectedly also abolished human complement lysis while the FcγRIII binding is retained (See entire document, page 320, column 1, first paragraph, in particular).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of guidance and in vivo working examples, predicting what changes can be made to the amino acid sequence in the effector domain of any human immunoglobulin that after insertion and/or modification will retain both structure and have similar function is unpredictable,

Furthermore, it is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular).

Riechmann *et al*, of record, teach the effector functions of human IgG3 is less effective in both complement and cell-mediated lysis while IgG2 isotype is weakly lytic and IgG4 is non-lytic (See page 326, Heavy-chain constant domains, in particular). Given the lack of guidance as to the binding specificity of the binding molecule, it is unpredictable which undisclosed binding molecule would bind to which target associated with which disorder, in turn, would be useful as for a method for treating all disease in the absence of vivo working example.

With regard to pharmaceutical preparation as recited in claims 40 and 49, the specification does not adequately teach how to effectively treat all disorder using the undisclosed binding molecule. The specification disclosed only binding molecule that binds to CD52 and FOG-1. The specification does not teach how to extrapolate data obtained from in vitro binding assays and inhibition of complement mediated cell lysis in vitro to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Thus it is not clear that the skilled artisan could predict the efficacy of all binding molecules exemplified in the specification for treating all disorder commensurate in scope as encompassed by the claims.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/26/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the Examiner's attempt to allow only a preferred embodiment is inappropriate, especially where the specification teaches one of ordinary skill

know how to make and use the presently claimed invention. (2) The specification "discloses" several biding domain page 15, lines 1 to page 24, line 17, example 7. (3) If the applicants were indeed explicitly claiming that each claimed binding molecule was able to treat any disease, then that might be grounds for objection. But there is nothing in the claims or the specification to support such interpretation. (4) The examiner has not provide any evidence or technical reasoning substantiating the fact that the binding molecules including antibody binding sites cannot be made or used. The modified effector regions were (of necessity) demonstrated using two different particular binding domains since this was the only way of demonstrating the effector activities, but there is absolutely no evidence or technical reasoning to support the idea that the inhibitory activities could not be achieved using other targets and binding domains. (5) It is well established that constant regions can be mixed and matched with variable binding domains (see e.g. Clark, 1997 of record - pg 88, 9th line from bottom - "immunoglobulips exist as J...C region domains associated with visually any of the possible V regions"). It is therefore entirely conventional in this area of technology that inventions made in respect of constant regions should be claimed without reference to variable regions and vice versa. See, for example the claims of the Genentech cases cited in the attached Information Disclosure Statement (i.e., WO 99/51642 and U.S. Patent No. 6,194,551). (6) The section of the specification cited by the examiner on page 9, lines 20-25, very clearly refers to the modifications made in the present application at positions 233-236 & 327, 330-1 with respect to the wild-type. Further, claim 32 has now amended to recite "98% limitation" as per claim 41. (7) In respect of Ngo et al., the applicants note, for completeness, that the applicants are not attempting to define structure purely by reference to activities In any case, by contrast with Ngo et al, the crystal structure of IgG is known (e.g. Clark, 1997 of record- page 92 and legend page 93), and there is a considerable literature on the subject. In the light of this and the present disclosure it would be possible for the "ordinarily skilled person to predict residues Which are non=sacrosanct in the claims, and which would not be expected to destroy activities, e.g. because they were not near the sacrosanct residues, or because they were conservative substitutions. The reference to Kuby et al appears to the applicants to be irrelevant since it does not seem to be concerned with engineering immunoglobulins. (8) The breadth of the claims: all claims are based on natural CH2 regions in which mutations have been introduced such as to give specific amino acids at positions 233-236 & 327, 330-1. Such molecules have been compared with other mutations at those positions and wild type immunoglobulins and the particular mutations have been shown to result in a desirable

combination of activities (which result was not obvious from the prior art - see comments below). The claims define CH2 regions in which these precise amino acids have been introduced. (9) The nature of the invention: the invention is in the field of engineering immunoglobulins. The art and level of skill in this art was advanced at the time of the present invention. (10) The state of the prior art: there is a considerable literature in the field of 'engineering immunoglobulins, albeit that none of the art taught or suggested the precise combination of residues of the present claims. Since the specification need not disclose what is well-known to those of ordinary skill in the art, and preferably omits that which is well-known to those of ordinary skill and already available to the public. (11) The level of one of ordinary skill: in terms of the ability to prepare and test mutants for different activities this is high - as evidenced by many of the publications of record, including those relied upon in the final rejection (albeit that none of these suggested the presently claimed mutants). It is thus clear that in the light of the present disclosure, immunoglobulins comprising the precisely defined mutations of the claimed invention could be prepared without undue burden, and if required further mutations could be introduced (e.g. to match known allotypes). Similarly such constant regions could be combined with different binding domains by those skilled in the ad without undue burden. (12) Amount of Direction or Guidance Present: Sufficiency of Disclosure/predictability/ Non-predictability: As a generality, the applicants accept that changes to primary structure can affect higher order structure and activity in ways which are not always certain. In the present case mutations in the 233-236 & 327, 330-1 region were prepared in 8 different combinations, which were compared with each other and 3 different wild-type immunoglobulins in many different experiments (see e.g. Figures 1 to 14) including more than one variable region for increased confidence. The consistent results were that immunoglobulins including the claimed combinations of residues gave the required properties in both IgG1, 2 and 4 backgrounds and irrespective of which binding domain was used. Since the claimed subject is based on said mutations in said backgrounds, it will be clear to one of ordinary skill in the art that sufficient direction is provided to practice the presently claimed invention. Additionally the applicants submit that it would be inequitable to insist upon recitation in the claims of only the precisely recited sequences. Respect to c) Pharmaceutical preparations in vivo examples General, At the outset, and referring to Riechmann et al. page 323, abstract and 1st paragraph, it is clear that immunoglobulins (both naturally occurring in serum, and engineered) had been used as therapeutics for over 100 years prior to the date of the present application. A list of "modified" therapeutic antibodies undergoing clinical trials in humans can be found at: hdpr//-

.path.cam.ac.uw-mrc7/humanisation/antibodies.html. There can be no question therefore that immunoglobulins have been, and can be, used as therapeutics. With regard to In vitro - in vivo, the presently claimed molecules have been tested for numerous effector functions as described in Figures 1 to 14 and Examples 1 to 6b. Moreover, they have been shown to inhibit the response of monocytes to immunoglobulins sensitized cells and inhibit the killing of targeted cells through complement lysis or ADCC. As discussed in the Examples e.g. page 49, Lines 30-34, the tests used have been those already shown to be useful in predicting in vivo pathology. The tests on page 50 studied CL responses which were indicative of haemolytic disease in the newborn.

However, the scope of the claims are drawn to any or all binding molecules comprising the binding domain of all antibody and any or all effector domain that is any chimeric domain derived from two or more human immunoglobulin heavy chain CH2 domains wherein the chimeric domain is human heavy chain CH2 domain which has amino acids at the stated positions 233P, 234V, 235A, 236G, 327G, 330S and 331S and is at least 98% identical to any CH2 sequence (residues 231-340) from human IgG1 or IgG4 for treating a patient with all disorder such as the ones recited in claim 28 or to interfere with the binding of any second binding molecule to the undisclosed target molecule (claim 25).

The specification discloses only two binding molecules comprising a binding domain selected from the group consisting of CD52 and FOG-1 (RhD antigen on RBC) and an effector domain wherein the CH2 domain is SEQ ID NO: 3 or 12 as shown in Figure 17 and has reduced affinity for FcγRI, FcγRIIa or FcγRIII, a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The specification further discloses the effector domain consisting of CH2 domain from human immunoglobulin IgG1 substituting for CH2 domain from either IgG2 or IgG4 wherein the amino acid residue E at position 233 of CH2 domain of human IgG1 is substituted for P where P corresponds to the position 233 of the CH2 domain of human IgG2. The amino acid residue L at position 234 of CH2 domain of human IgG1 is substituted for V where V corresponds to the position 234 of the CH2 domain of human IgG2. The amino acid residue L at position 235 of CH2 domain of human IgG1 is substituted for A where A corresponds to the position 235 of the CH2 domain of human IgG2. The amino acid residue G at position 236 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 236 of the CH2 domain of human IgG4. As an alternative, the amino acid residue G at position 236 of CH2 domain of human IgG1 is deleted since G corresponds to the position 236 of the CH2 domain of human

IgG2 is lacking. The amino acid residue A at position 327 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 327 of the CH2 domain of human IgG2. The amino acid residue A at position 330 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 330 of the CH2 domain of human IgG4. The amino acid residue P at position 331 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 331 of the CH2 domain of human IgG4 (See Figure 15). The specification defines binding domain may derive from the same source or a different source to the effector domain wherein binding domain may bind to any target (e.g. carbohydrate, lipid such as phospholipids or nucleic acid (See page 15, lines 6-12). The specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21).

Other than the specific binding molecule mentioned above, the specification does not teach how to make *all* binding molecules (claims 32-33, 35, 37-39, 41-42, and 44, 46-48) and pharmaceutical composition comprising all binding molecules (claims 40 and 49). Let alone a method for treating all disease (claim 28) because of the following reasons.

First, there is insufficient guidance as to the *binding specificity* of all binding molecule or the target to which all the binding molecule bind. Second, there is insufficient guidance about the structure of the "effector domain", the "chimeric domain", the "two or more human CH2 domains", and "the binding molecule" without the amino acid sequence (claims 32, and 41). Third, there is insufficient guidance as to which combination of "at least one amino acid" within which "region of the CH2 domain" of which human immunoglobulin has been modified by amino acid substitution, deletion, or addition to the corresponding amino acid from which second, different human immunoglobulin heavy chain CH2 domain such that the resulting effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII by comparison to which first or second human immunoglobulin heavy chain CH2 domains (claim 35). Fourth, there is insufficient guidance as to which combination of "at least one amino acid" within which "region of the CH2 domain" of which human immunoglobulin has been modified by amino acid substitution, deletion, or addition to the corresponding amino acid from which second, different human immunoglobulin heavy chain CH2 domain that the effector domain has a reduced complement lysis by comparison to which first or second human immunoglobulin heavy chain CH2 domains (claim 35).

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Without the amino acid sequence, one skill in the art cannot make, much less use the claimed invention.

Kuby *et al*, of record, teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Since the *binding specificity* of the binding molecule, the amino acid sequence of the "binding molecule" and the "effector domain" are not enabled, it follows that the nucleotide sequence encoding the effector domain (claim 16), the binding molecule (claim 17) without nucleic acid sequence are not enabled. Fifth, the specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21). However, the cDNA, RNA, genomic DNA or modified DNA encoding the claimed binding molecules are not disclosed, much less cDNA, RNA, genomic DNA and modified nucleic acid or nucleic acid analog encoding all binding molecules. Since the nucleic acid sequence encoding the effector domain or the binding molecule are not enable, it follows that the vector and host cell comprising said undisclosed nucleic acid sequence encoding all binding molecule are not enabled. In addition to the lack of guidance as to structure of nucleotide sequence encoding all the binding molecule, there is insufficient guidance as to which nucleotides that corresponds to which 2, 3 or 4 amino acids in which first human immunoglobulin heavy CH2 domain in at least which one region such as 233-236 and 327-331 of which CH2 domain to be modified to corresponds to which nucleotides corresponding to which amino acids from which second human immunoglobulin. The recitation of the EU numbering system without the amino acid sequence and/or nucleotide sequence has no structure. Further, there is insufficient guidance as to which amino acids, the corresponding nucleotides to be substitute for which undisclosed amino acids, the corresponding nucleotides and whether the resulting effector domain of the binding molecule maintains its structure and functions. Given the indefinite number of binding molecules, there is insufficient working examples demonstrating that all undisclosed binding molecule having various amino acids substitution at the CH2 domain would bind FcγRIIb and cause inhibition of one or more B cell activation, mast cell degranulation, or phagocytosis. Further, there is insufficient working example demonstrating that the claimed

method of using all undisclosed binding molecule could prevent, inhibit, or interfere with the binding of any undisclosed second binding molecule such as any antibody to which target molecule. Further, there is a lack of in vivo working example demonstrating all undisclosed binding molecule could treat all disorders such as graft-vs-host disease, host-vs-graft disease, organ transplant rejection, bone-marrow transplant rejection, all autoimmune disorder such as vasculitis, autoimmune haemolytic anaemia, autoimmune thrombocytopenia, arthritis, fetal/neonatal alloimmune thrombocytopenia, asthma, allergy, all chronic acute inflammatory disease such as Chrohn's, HDN, Goodpastures, sickle cell anaemia, and coronary artery occlusion.

Even if the binding molecule wherein the binding domain is limited to CD52 and FOG-1 and the effector domain is limited to SEQ ID NO: 1-3, the specification discloses on page 55 line 46 that "the effect of mutations cannot always be predicted from wildtype antibody activities but will depend on the novel context (based on 'mixed' subclasses of IgG) in which the mutation is present". The specification further discloses that the binding molecule wherein the effector domain such as G1Δb (SEQ ID NO: 1) and G1Δc (SEQ ID NO: 2) have 50 to 10 fold lower complement mediated lysis, respectively, although both G1Δb (SEQ ID NO: 1) and G1Δc (SEQ ID NO: 2) bind to the receptor FcγRII equally (See page 55, last full paragraph).

Mogan *et al* (PTO 1449) teach that changing the Leu235 to Glu in the N-terminal end of the C_H2 domain abolished FcγRI binding and unexpectedly also abolished human complement lysis while the FcγRIII binding is retained (See entire document, page 320, column 1, first paragraph, in particular).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of guidance and in vivo working examples, predicting what changes can be made to the amino acid sequence in the effector domain of any human immunoglobulin that after insertion and/or modification will retain both structure and have similar function is unpredictable, Furthermore, it is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular).

Riechmann *et al*, of record, teach the effector functions of human IgG3 is less effective in both complement and cell-mediated lysis while IgG2 isotype is weakly lytic and IgG4 is non-lytic (See page 326, Heavy-chain constant domains, in particular). Given the lack of guidance as to the binding specificity of the binding molecule, it is unpredictable which undisclosed binding molecule would bind to which target associated with which disorder, in turn, would be useful as for a method for treating all disease in the absence of vivo working example.

With regard to pharmaceutical preparation as recited in claims 40 and 49, the specification does not adequately teach how to effectively treat all disorder using the undisclosed binding molecule. The specification disclosed only binding molecule that binds to CD52 and FOG-1. The specification does not teach how to extrapolate data obtained from in vitro binding assays and inhibition of complement mediated cell lysis in vitro to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Thus it is not clear that the skilled artisan could predict the efficacy of all binding molecules exemplified in the specification for treating all disorder commensurate in scope as encompassed by the claims.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Until the binding specificity of all binding molecules are enabled, the specification as written merely extends an invitation for one skill in the art for further experimentation to arrive at the claimed invention.

11. Claims 16-29, 32-33, 35, 37-42, 44, and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) the binding specificity of any or all binding molecules as set forth in claims 32-33, 35, 37-39, 41-42, 44, and 46-48, (2) all isolated nucleic acid encoding all binding molecules as set forth in claims 16-19, (3) host cell comprising any undisclosed nucleic acid as set froth in claim 20, (4) a method for producing any or all binding molecule by *modifying* any or all nucleotide sequence as et forth in claims 21-22, (5) any pharmaceutical composition comprising any or all binding molecule as set forth in claims 40 and 49, (6) a method of binding all target molecule comprising contacting any

target molecule as set forth in claims 23-27 and (7) a method of treating any disorder such as the ones recited in claim 28 using all binding molecule.

The specification discloses only two binding molecules comprising a binding domain selected from the group consisting of CD52 and FOG-1 (RhD antigen on RBC) and an effector domain wherein the CH2 domain is SEQ ID NO: 3 or 12 as shown in Figure 17 and has reduced affinity for FcγRI, FcγRIIa or FcγRIII, a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The specification further discloses the effector domain consisting of CH2 domain from human immunoglobulin IgG1 substituting for CH2 domain from either IgG2 or IgG4 wherein the amino acid residue E at position 233 of CH2 domain of human IgG1 is substituted for P where P corresponds to the position 233 of the CH2 domain of human IgG2. The amino acid residue L at position 234 of CH2 domain of human IgG1 is substituted for V where V corresponds to the position 234 of the CH2 domain of human IgG2. The amino acid residue L at position 235 of CH2 domain of human IgG1 is substituted for A where A corresponds to the position 235 of the CH2 domain of human IgG2. The amino acid residue G at position 236 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 236 of the CH2 domain of human IgG4. As an alternative, the amino acid residue G at position 236 of CH2 domain of human IgG1 is deleted since G corresponds to the position 236 of the CH2 domain of human IgG2 is lacking. The amino acid residue A at position 327 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 327 of the CH2 domain of human IgG2. The amino acid residue A at position 330 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 330 of the CH2 domain of human IgG4. The amino acid residue P at position 331 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 331 of the CH2 domain of human IgG4 (See Figure 15). The specification defines binding domain may derive from the same source or a different source to the effector domain wherein binding domain may bind to any target (e.g. carbohydrate, lipid such as phospholipids or nucleic acid (See page 15, lines 6-12). The specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21).

With the exception of the specific binding molecule mentioned above, there is inadequate written description about the *binding specificity* of all binding molecules as claimed. Further, there is inadequate written description about any isolated nucleic acid as set forth in claims 16-19

for all binding molecules without the nucleotide sequence. The specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21). However, the cDNA, RNA, genomic DNA or modified DNA encoding any or all binding molecules or effector domain have not been described. Since the nucleic acid sequence encoding the effector domain and the binding molecule are not adequately described, it follows that the vector and host cell comprising said undisclosed nucleic acid sequence encoding all binding molecule are not adequately described. In addition to the lack of a written description about any of nucleotide sequence encoding all the binding molecules, there is insufficient written description about which nucleotides that correspond to which 2, 3 or 4 amino acids in which first human immunoglobulin heavy CH2 domain in at least which one region such as 233-236 and 327-331 of which CH2 domain to be modified to corresponds to which nucleotides corresponding to which amino acids from which second human immunoglobulin. The recitation of the EU numbering system without the amino acid sequence and/or nucleotide sequence of the wild type has no structure. Further, there is insufficient written description about which amino acids, the corresponding nucleotides to be substitute for which undisclosed amino acids and the corresponding nucleotides and whether the resulting effector domain of the binding molecule maintains its structure and functions.

Given the indefinite number of binding molecules, the binding specificity of all binding molecules is not adequately described. Further, the specification discloses only two binding domain such as FOG-1 and anti-CD52 and four specific CH2 domains such as the ones shown in Figure 17 for in vitro inhibition assays. Given the lack of a written description of *any* additional representative species of (1) binding domain, and (2) effector domain, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/26/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the above comments equally well apply in response to the Examiner's remarks which appear to be similar in their basis in relating to the enablement rejection. The Examiner is requested to not that the specification describe several binding domains e.g. page 15, line 1-page 24, line 17, Example 7. The examiner is request to respond to example 16 of the synopsosis of application. The present claims provide just such a combination of structure and functional characteristics. In the example given in the Guidelines, an antibody described purely by its binding specificity was deemed to satisfy the Written description requirement. The present case discloses several example constant regions and a narrow genus is claimed based closely on these. Thus, compared with the Example 16 in the Guideline, it contains considerably more information in support of a claim containing many more limitations.

In response to applicant' argument that the present claims provide a combination of structure and functional characteristics, it is noted none of the claims describe the **binding specificity** of all binding molecules.

The scope of the claims are drawn to any or all binding molecules comprising the binding domain of all antibody and any or all effector domain that is any chimeric domain derived from two or more human immunoglobulin heavy chain CH2 domains wherein the chimeric domain is human heavy chain CH2 domain which has amino acids at the stated positions 233P, 234V, 235A, 236G, 327G, 330S and 331S and is at least 98% identical to any CH2 sequence (residues 231-340) from human IgG1 or IgG4 for treating a patient with all disorder such as the ones recited in claim 28 or to interfere with the binding of any second binding molecule to the undisclosed target molecule (claim 25).

The specification does not reasonably provide a **written description** of (1) the binding specificity of any or all binding molecules as set forth in claims 32-33, 35, 37-39, 41-42, 44, and 46-48, (2) all isolated nucleic acid encoding all binding molecules as set forth in claims 16-19, (3) host cell comprising any undisclosed nucleic acid as set froth in claim 20, (4) a method for producing any or all binding molecule by *modifying* any or all nucleotide sequence as et forth in claims 21-22, (5) any pharmaceutical composition comprising any or all binding molecule as set forth in claims 40 and 49, (6) a method of binding all target molecule comprising contacting any target molecule as set forth in claims 23-27 and (7) a method of treating any disorder such as the ones recited in claim 28 using all binding molecule.

The specification discloses only two binding molecules comprising a binding domain selected from the group consisting of CD52 and FOG-1 (RhD antigen on RBC) and an effector

domain wherein the CH2 domain is SEQ ID NO: 3 or 12 as shown in Figure 17 and has reduced affinity for FcγRI, FcγRIIa or FcγRIII, a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The specification further discloses the effector domain consisting of CH2 domain from human immunoglobulin IgG1 substituting for CH2 domain from either IgG2 or IgG4 wherein the amino acid residue E at position 233 of CH2 domain of human IgG1 is substituted for P where P corresponds to the position 233 of the CH2 domain of human IgG2. The amino acid residue L at position 234 of CH2 domain of human IgG1 is substituted for V where V corresponds to the position 234 of the CH2 domain of human IgG2. The amino acid residue L at position 235 of CH2 domain of human IgG1 is substituted for A where A corresponds to the position 235 of the CH2 domain of human IgG2. The amino acid residue G at position 236 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 236 of the CH2 domain of human IgG4. As an alternative, the amino acid residue G at position 236 of CH2 domain of human IgG1 is deleted since G corresponds to the position 236 of the CH2 domain of human IgG2 is lacking. The amino acid residue A at position 327 of CH2 domain of human IgG1 is substituted for G where G corresponds to the position 327 of the CH2 domain of human IgG2. The amino acid residue A at position 330 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 330 of the CH2 domain of human IgG4. The amino acid residue P at position 331 of CH2 domain of human IgG1 is substituted for S where S corresponds to the position 331 of the CH2 domain of human IgG4 (See Figure 15). The specification defines binding domain may derive from the same source or a different source to the effector domain wherein binding domain may bind to any target (e.g. carbohydrate, lipid such as phospholipids or nucleic acid (See page 15, lines 6-12). The specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21).

With the exception of the specific binding molecule mentioned above, there is inadequate written description about the *binding specificity* of all binding molecules as claimed. Further, there is inadequate written description about any isolated nucleic acid as set forth in claims 16-19 for all binding molecules without the nucleotide sequence. The specification defines nucleic acid may include cDNA, RNA, genomic DNA (including introns) and modified nucleic acids or nucleic acid analogs (page 23, lines 18-21). However, the cDNA, RNA, genomic DNA or modified DNA encoding any or all binding molecules or effector domain have not been

described. Since the nucleic acid sequence encoding the effector domain and the binding molecule are not adequately described, it follows that the vector and host cell comprising said undisclosed nucleic acid sequence encoding all binding molecule are not adequately described. In addition to the lack of a written description about any of nucleotide sequence encoding all the binding molecules, there is insufficient written description about which nucleotides that correspond to which 2, 3 or 4 amino acids in which first human immunoglobulin heavy CH2 domain in at least which one region such as 233-236 and 327-331 of which CH2 domain to be modified to corresponds to which nucleotides corresponding to which amino acids from which second human immunoglobulin. The recitation of the EU numbering system without the amino acid sequence and/or nucleotide sequence of the wild type has no structure. Further, there is insufficient written description about which amino acids, the corresponding nucleotides to be substitute for which undisclosed amino acids and the corresponding nucleotides and whether the resulting effector domain of the binding molecule maintains its structure and functions.

Given the indefinite number of binding molecules, the binding specificity of all binding molecules is not adequately described. Further, the specification discloses only two binding domain such as FOG-1 and anti-CD52 and four specific CH2 domains such as the ones shown in Figure 17 for in vitro inhibition assays. Given the lack of a written description of *any* additional representative species of (1) binding domain, and (2) effector domain, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 16-29, 32, 33, 35, 37-42, 44, and 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "...binding molecule capable of specifically binding FcγRIIb and optionally FcRn" in claim 32 line is ambiguous because the specification discloses that it is the *effector domain* of the binding molecule, not the binding molecule that is capable of binding to FcγRIIb and optionally FcRn without triggering significant complement dependent lysis or cell mediated destruction of the target. The claim as written suggests that the binding domain of the binding molecule is capable of binding to FcγRIIb and optionally FcRn instead of the effector domain.

The "numbered with respect to the EU system of Kabat" in claims 32 and 41 is ambiguous and indefinite because the wild type sequence to which the amino acids at the stated position come from is not disclosed.

The "homologous to part of a constant domain of a human immunoglobulin heavy chain" in claim 41 is indefinite and ambiguous because it is not clear which part of the effector domain is homologous to which human immunoglobulin heavy chain. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "G1Δab or G2Δa" in claim 42 is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct products.

The "effector domain" is SEQ ID NO: 3 or SEQ ID NO: 12 as shown in Figure 17 is ambiguous and indefinite because SEQ ID NO: 3 and SEQ ID NO: 12 in Figure 17 are only **CH2 domains** of the effector domain of a binding molecule. The "effector domain" of a binding molecule or antibody contains CH1, CH2, CH3 and CH4 domains.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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